

## IMMUNOLOGICAL PHENOMENA OF SYPHILIS\*†

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The decrease in the incidence of syphilis after the war led some of us to suppose that the disease might pass from our notice without our ever having explained its protean manifestations. The efficacy of penicillin and the volume of it given to early cases today compared with 20 years ago means that younger venereologists may never see infectious relapse which once was commonplace. On the other hand, the recent increase in early syphilis suggests that we should be on our guard for second infections and may yet give clinicians a chance to get to grips with a subject in some measure comparable with the painstaking efforts of the experimental syphilologists.

### The Problem

It is generally accepted that in man there is no natural immunity to syphilis, but that there are degrees of resistance clearly shown by the different degrees of mildness and severity of the disease as seen in the clinic. It needs no stretch of the imagination to conceive a mildness amounting to no more than that of a symptomless carrier as suggested by Kolle (1928) and by Prigge (1931), just as one recognizes at the other end of the scale the fatal toxæmia of the syphilitic marasmic infant. Many observers have remarked on the decreasing severity of syphilis throughout the years when comparing their own observations with those of writers of the last and previous centuries. We may be witnessing an evolutionary adaptation of man to the *Treponema pallidum* even without taking into account the efficacy of modern treatment. However, there are no available statistics nor is there any epidemiological evidence to prove natural immunity in man, with the following possible exceptions.

First, Brandt (1922) found that 74 out of 1,169 prostitutes showed no evidence of syphilis during

periods of observation extending from 2 to 10 years. These women may not have been exposed to infection or they may have suppressed the virus with stovarsol, as suggested by Harrison (1929).

A second observation is that of von Werssowetz (1948) who stated that 50 per cent. of the named contacts of primary and secondary syphilis escaped infection.

A third observation, of little relevance since the advent of penicillin is that it was not uncommon to find patients who had had more attacks of gonorrhoea than figured in the prevailing ratio of gonorrhoea to syphilis.

In the absence of proof to the contrary, therefore, we should not dismiss as non-existent, the possibility of natural immunity to syphilis in man.

It is agreed that there is no known method of imparting immunity to syphilis to man short of letting him acquire the disease. Immunity to syphilis is derived from infection. Our problem is to find out in what circumstances and for how long this immunity remains when once established, and in what circumstances it fades, disappears altogether, or is prevented from developing. In our pursuit of information on these points we encounter other problems of absorbing interest as, for example, the differing degrees of immunity at different stages of the disease and in different tissues of the body; the localization of the immune process in the body fluids or cells; the mechanism of its formation; its relation to hypo- and hypersensitivity; its relation to the reagin responsible for the Wassermann reaction; the part played by treponemal immobilizing antibodies. In a veritable forest of facts, speculations, and theories, we may be forgiven for pausing briefly to meditate upon the very nature of disease itself and to challenge ourselves to define what the word "syphilis" really means.

A host of questions faces us but a paper of this

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length is yet too brief for us to attempt more than an answer to three.

- (1) When can a second inoculation of *T. pallida* succeed in infecting the host?
- (2) How can we account for the paradox to which Neisser called attention in 1884, namely that man may be refractory to exogenous *T. pallida* but susceptible to endogenous *T. pallida*—may resist re-infection but suffer relapse from his own *T. pallida*, often after years of indifference to them?
- (3) How can we account for the discrepancy in the size and severity of lesions as typified by the primary chancre, the secondary macule, and the tertiary gumma; why are *T. pallida* so prolific in condylomata lata and so sparse in gummata?

At the outset a distinction must be recognized between, on the one hand, resistance to organisms, whereby *T. pallida* are dealt with at their point of entry as in the subject who is immune to natural or experimental re-infection and whereby spontaneous cure may follow infection; and, on the other hand, tolerance of organisms, as is manifest in latent syphilis and whereby asymptomatic re-infection and possibly asymptomatic primary infection is explained. This distinction is more than academic. The possibility of re-infection seems remote to the patient. He sees to that. But with a superficial lay knowledge of the disease he is appalled at the thought of incurability. The Sword of Damocles is a not uncommon cause of mental disease.

#### Historical Observations

From time to time there have appeared excellent papers on the subject of relapse and re-infection in syphilis, many of them reviewing the subject historically and bringing up to date our knowledge of experimental syphilis. Among them may be mentioned those of Hutchinson (1895a), Chesney (1927, 1930), Halley and Wassermann (1928), Harrison (1929), Stokes, Schoch, and Ireland (1931), Moore (1945), Beerman (1946), Urbach and Beerman (1947), Gueft and Rosahn (mouse syphilis) (1948), and Magnuson and his colleagues (1948). This historical section has been compiled by reference to these papers and the reader is referred to them for further information on experimental syphilis, a resumé of which, largely taken from Harrison (1929), is given below in a later section.

Hunter (1810) showed that secondary syphilitics could not be successfully re-inoculated with material from their own sores and wrongly concluded that the lesions of secondary syphilis were non-infectious. In Hunter's day hard and soft sores were all regarded as

syphilitic. Ricord, in the early 19th century, showed lack of resistance upon auto-inoculation of soft sores and demonstrated the difference between chancres and chancroids. He propounded the theory that syphilis conferred lifelong immunity. Fournier (cited by Hutchinson, 1895) never saw a second attack of syphilis. Rollet (1865) recognized that successful re-inoculation was possible during the incubation period, but that with the appearance of the chancre immunity was an accomplished fact.

Thus the earliest notion was that second infections of syphilis were commonplace. The next idea was that syphilis gave lasting immunity. It was then assumed that cure was the rule. At the turn of the century the chronic nature of the disease was well recognized. Neisser (1884) elaborated the idea that immunity to syphilis was due to the presence of infection and that syphilis was seldom cured. It was recognized that the supposedly cured patient could be re-infected and that the uncured could relapse.

Hutchinson (1895b) observed the frequency of relapsing chancres and noted their occurrence within 2 years of the first infection. Once it was recognized that chancres relapsed, that cure was infrequent, and that infection spelt immunity, the whole notion of re-infection was disparaged almost to vanishing point. But Hutchinson (1895) hung on and admitted the difficulty or even impossibility of differentiating between mono-recidives (as we call them) and re-infections. He called them all "second infections", to-day we should perhaps call them "second episodes".

#### Conflicting Concepts and a Die-hard Dogma

With the first transmission of syphilis to animals in 1903, the discovery of *Treponema pallidum* in 1905, and the introduction of organic arsenicals for the treatment of syphilis in 1909, the study of the disease "found its inspiration primarily in the laboratory". And in the laboratory arose the concepts of immunity and the dogma which dominated the interpretation of clinical phenomena for the next 40 years or so.

The first doctrine was that propounded by Neisser (1884). As rarity of re-infection was attributed to rarity of cure, he showed in apes not only that biological cure could be effected but that treated animals could be re-infected with chancre formation. He asserted that successful second inoculation implied eradication of the first infection and conversely that failure to re-infect implied persistence of the first infection which accounted for the resistant state. Hence re-infection was regarded as proof of cure. Kolle (1924, 1928) showed that rabbits treated within 45 days of the first infection were invariably

successfully re-inoculated—those treated after the 90th day almost never. He asserted that rabbits treated early were cured—those treated late were not. (It seems pertinent at this point to reflect upon the effect that this doctrine, together with the fixed positive Wassermann reaction, has had on the management of human syphilis. For 50 years, physicians, with staggering zeal, have pumped countless kilograms of arsenic and bismuth and vanloads of penicillin into battalions of humans over much of their lives, with little effect other than boosting the clinic attendance figures and creating alarm or despondency in the breasts of their patients. As Wilfred Trotter remarked in another context, "It was more than truth that suffered".) Neisser's doctrine, then, was one of "infection immunity".

The second doctrine was that of Chesney and Kemp (1925) who proved that rabbits could be cured after the 90th day. They challenged Neisser's doctrine and postulated that immunity to syphilis persisted after cure. Immunity was a true immunity and did not depend upon the presence of spirochaetes for its continuance. Urbach and Beerman (1947) said that this distinction was artificial, for "protection of any kind is immunity". This comment was all very well for the laboratory but somewhat nonchalant for the clinic.

### Animal Experiments

The literature on animal experimentation, particularly concerning rabbits, is voluminous and a resumé is beyond the scope of this paper. In the development of the two opposing concepts just referred to, certain facts came to light. The following tabulated summary is largely quoted from Harrison (1929).

- (a) Shortly after the development of a primary lesion a second primary or similar lesion cannot be easily produced on re-inoculation. This involves the original Neisserian concept of "anergie" or resistance and chancre immunity.
- (b) This "chancre immunity" is dependent on the reaction of tissues and not on the mere presence of the organism.
- (c) Inoculation in certain tissues (*e.g.* the cornea) does not protect against inoculation in other sites (*e.g.* the testis), but certain tissue inoculations have greater protective value than others.
- (d) An animal may harbour a syphilitic infection without reacting to it.
- (e) In rabbits made carriers of infection by intravenous inoculation, the lymph nodes are infected. In such rabbits typical syphilomata of the testes will develop when these are subsequently inoculated with the same strain of *T. pallidum*.
- (f) Re-inoculation of a rabbit on the site of a previous testicular chancre is met with decreasing success as the age of the first infection increases when a homologous strain of spirochaetes is used. Heterologous strains meet with greater success even after the 90th day in a proportion of rabbits.
- (g) Non-appearance of clinical lesions in animals after re-inoculation is not proof of failure to re-infect.
- (h) "Chancre immunity" is similar to the slowly-developed absolute immunity which comes later in the disease but is less in degree so that, with "chancre immunity" only, asymptomatic re-infection is possible. I, personally, dispute this statement.
- (i) Curative treatment of the first infection cuts short the development of immunity while it *is* developing but does not affect it after it has developed. Thus, the success of re-inoculation of treated animals depends not on the fact that treatment has been successful but on the stage of the first infection at which the treatment was commenced.
- (j) Reference has been made to the strain of spirochaete used and the site of re-inoculation. Of other factors affecting the result of re-inoculation, the most important is the size of the challenging inoculation. Magnuson, Eagle, and Fleischman (1948) and Magnuson, Rosenau, and Clark (1948) approached the subject quantitatively, and showed immunity in rabbits to be a measurably progressive affair. Challenging inocula resulted in symptomatic re-infection, asymptomatic re-infection, or no re-infection, according to the duration of the original infection *and* the size of the challenging inoculum.
- (k) The lesions produced on re-inoculation tend to take on the characteristics pertaining to the stage reached by the first infection. Especially is this so in man, as will be explained below.
- (l) Nearly all these experiments involve the use of a needle. Deposition of the syphilitic virus in the sub-preputial sac of the infected rabbit produces second lesions much less frequently. In other words, injection of spirochaetes favours the spirochaetes, mere contagion favours the host. I am convinced that this fact accounts for the rarity of re-infection in man.

### Human Experiments

Frequent references to the literature on human re-inoculation experiments occur in Chesney's monograph (1927), in a comprehensive review by Beerman (1946), and in the report by Magnuson, Thomas, Olansky, Caplan, DeMello, and Cutler (1956) of their Sing Sing experiments. The following summary has been composed from these three papers.

Chancres can be produced in man while the first chancre is progressing, success in the secondary stage produces papules and in the tertiary stage, gummata. Bizzozero and Bernucci (1928) drew attention to this from their experiments on 106 patients. Hashimoto (1926) produced dark-ground positive lesions with or without subsequent secondary manifestations and dark-ground negative papules in patients with various categories of treated syphilis.

In general, immunity to chancre formation is well marked in latency. Dark-ground positive secondary papules have been observed, as well as gummata. This immunity lessens with the passage of time.

In late syphilis, Finger and Landsteiner (1912) produced gummata on re-inoculation of patients with tertiary skin lesions. So did Queyrat and Pinard (1909). Pasini noted different results in the same patient re-inoculated at different sites and suggested that local tissue immunity was a factor influencing the results. The incubation period of these tertiary successes was shorter than the secondary ones and this is much as we should expect. Either they were dealing with lessened immunity to which the tertiary lesions themselves stood witness or the inocula must have been large to produce results. Probably both factors were at work. A third factor is that tertiary lesions are allergic hypersensitive responses which by their nature tend to be prompt in onset.

In neurosyphilis, Truffi (1931) noted almost complete refractoriness to second inoculation of the skin of paretics—he found one positive report only. Prigge and Rutkowski showed immunity to be only skin-deep in paretics—spirochaetes passing to the lymph nodes. This seems to me an interesting prelude to the work of our latter-day French colleagues (Collart, Borel, and Durel, 1964), who have recently demonstrated spirochaetes in the lymph nodes of treated paretics. Lisi (1934) produced a dark-ground-positive syphiloma with adenopathy, followed by a roseolar then papulo-lenticular eruption and an increased reagin titre, in a parietic. After treatment these superimposed lesions disappeared, but the positive cerebrospinal fluid, general condition, and mental state remained the same.

Positive lesions have been produced in tabetics.

Immunity in congenital syphilis is only relative. Mestchersky and Bogdanof (1923) produced clinically-positive but dark-ground-negative lesions in fifteen out of eighteen patients, and these lesions responded to specific treatment. In Truffi's clinic, gummata were produced by inoculation in two congenital cases already showing gummata, one of which was dark-ground-positive.

Piccardi and Brunetti produced dark-ground-positive lesions followed by generalized symptoms in

two patients intensively treated in the primary stage. One of these had a weak positive Wassermann reaction at the time of re-inoculation.

It will be noted that all these human experiments, except the last, have been or seem to have been successful attempts at super-infection, and it was for long assumed that they would not lightly be repeated. With confidence in the curative power of penicillin, Magnuson and others (1956) undertook controlled re-inoculation experiments on 54 volunteers in Sing Sing jail who had previously had treated or untreated syphilis and on eight non-syphilitic volunteers. Fairly heavy doses of virulent Nichols strain *Treponema pallidum* were inoculated. All the eight controls were infected. None of five untreated late latent cases was infected.

The results of inoculating previously treated cases were briefly as follows. Early cases were defined as having had primary, secondary, or latent syphilis of less than 2 years' duration, and in the present context I regret we were not told which of these cases was which. Eleven such early cases were challenged: nine developed dark-ground-positive lesions, two developed dark-ground-negative lesions, all developed a rise in serological titre, and all were considered to have been re-infected.

Of 26 previously treated late latent cases, ten were considered to be re-infected; one of these developed a dark-ground-positive lesion, one a gumma, and the remainder dark-ground-negative papules.

Three previously re-infected cases were challenged. All had had two syphilitic "episodes" with "adequate" treatment but again we were not told what the previous states were. One developed a dark-ground-positive lesion, one a dark-ground-negative lesion with an increased serological titre, and one was not re-infected.

Of five congenital cases, four were re-infected; one had a dark-ground-positive lesion and three had dark-ground-negative lesions associated with an increased serological titre. One of these dark-ground-negative lesions was a gumma, and this occurred in the only case showing stigmata of congenital infection.

Two patients with previously-treated asymptomatic neurosyphilis were challenged. Neither showed clinical or serological changes, but one developed headaches and a pleocytosis in the cerebrospinal fluid; it is doubtful whether or not he was re-infected.

In all the cases considered to be re-infected, indurated papules developed at the site of inoculation. Some were dark-ground-positive and some were dark-ground-negative. The dark-ground-positive lesions mostly occurred in those with previous

early syphilis and, of course, in all the controls. Some of the papules went on to ulceration, others to form gummata. Many regressed before treatment was instituted.

An interesting feature in eleven re-infected cases was the appearance of a satellite eruption surrounding the inoculation papule. These eruptions appeared as macules, then papules, and were like secondary syphilides, a number being corymbiform. Seven out of eleven satellite eruptions appeared in previously-treated early cases and only one in a control patient. This was on the day his secondary rash appeared. The authors of the experiment were puzzled by these eruptions. I am inclined to think that the relatively massive dose of spirochaetes inoculated resulted in a dispersal wave through the lymphatics.

Where secondary lesions occurred the authors state that they differed in no way from secondary lesions sexually acquired.

Many of these cases were accepted as re-infections on the basis of their increased serological reagin and TPI titres. It is evident that the mere presence of circulating antibodies does not, of itself, produce an immune state and this fact has proved to be no small embarrassment to me in the development of my thoughts on the subject matter of this paper. I am indebted to Dr W. Fowler for showing me the records of two recent dark-ground-positive re-infections in patients, who were recently well treated for primary syphilis in Birmingham and whose TPI tests were shown to be positive shortly before the appearance of their second episodes. Nevertheless, to quote the Sing Sing experimenters, "one does seem safe in concluding that, given a group of patients who had been previously treated for syphilis, those patients with low TPI and STS titres will probably be less resistant to challenge than those who have high TPI and high reagin titres". It is an essential part of my thesis that circulating antibodies are profoundly concerned with the clinical phenomena of syphilis.

### The Clinic

Let us now turn to what the clinic may teach us. Here we are presented with clinical material in the form of re-infection, relapse, or progression, all of which provide evidence of lack of immunity. What we do not know, would like to know, but may never know, is the extent to which treated or untreated, cured or uncured patients expose themselves with impunity to the risk of fresh infection, and to what extent treated or untreated latent cases, as evidenced by positive serology, actually harbour live spirochaetes. Our study of immunity is confined to patients who show none of it!

A further difficulty in the clinic is due to nature performing her experiments in a haphazard fashion. We cannot specify conditions. We cannot measure the severity of infection, still less the degree of immunity, in any one case. Syphilis may take 20 years to wreak its havoc. Details which seem important to us to-day may have borne no significance to physicians 20 years ago—so our own case notes are apt to be scanty.

Furthermore, in trying to interpret clinical phenomena, we must guard against regarding as anything but exact the analogy between the clinic and the laboratory. Rabbits are not followed up for 20 years. In their brief span no waning of immunity is observed as is the case with man. Nor do they wash themselves after possible risk. Once bitten twice shy, homo sapiens uses his intellect as well as his antibodies and, as we cannot calibrate the former, who knows how immune any one patient really is? We cannot be exact scientists but must rather indulge in philosophic speculation.

Chesney's contention, that immunity persists after cure, was until recently almost universally accepted but it did not refute Neisser's contention that re-infection meant cure. This assumption has been refuted by Moore (1945) and by Urbach and Beerman (1947). By definition, re-infection does imply cure but in practice little account has been taken of the possibility of super-infection or asymptomatic re-infection which are subjects of much guess-work. Most clinical papers on the subject of relapse or re-infection appear to be devoted to one or other of these two aspects of lack of immunity to syphilis. On the subject of re-infection are the papers of Halley and Wassermann (1928), Stokes, Schoch, and Ireland (1931), Schoch and Alexander (1943), Moore (1945), and Beerman (1946). On the subject of mucocutaneous relapse are the papers of Stokes, Besançon, and Schoch (1931), Stokes, Cole, Moore, O'Leary, Parran, and Wile (1931), and Pariser (1939). Stokes, Besançon, and Schoch (1931) noted that the literature showed ten titles on re-infection to one on relapse, whereas relapse was considered by them to be fourteen times as common as re-infection. On reporting the latter, the focus is usually on re-infection pointing to the success of treatment. If one subjects one's thinking to the dogma that re-infection means cure and if one asserts that one's treatment is successful, then logically one draws attention to re-infection in patients thus treated as evidence of the success of the treatment. Conversely, opponents of the treatment in question will assert that these so called re-infections are, in fact, relapses. Therefore, in claiming success in treatment, it is important to have criteria for the diagnosis of re-infection.

Stokes, Schoch, and Ireland (1931) listed seventeen rigid criteria which came under fire from Moore (1945). There were so many that two or more observers would seldom agree upon the differentiation between relapse and re-infection. Concerned then with the efficacy of penicillin, Moore (1945) urged clinicians still to adopt rigid criteria before diagnosing re-infection. Extravagant claims for penicillin were quite rightly to be avoided. This was well for students of penicillin but no help to the study of immunity.

On the other hand, the more of Stokes's criteria to which one attempts to adhere, the nearer to vanishing point becomes the apparent incidence of re-infection. The study of immunity in syphilis necessitated the adoption of the lax criteria of Halley and Wassermann (1928), of which there are but two: first, there must be proof of the first infection either by dark-ground demonstration of spirochaetes or by positive serology; second, after an interval following antisyphilitic treatment there must develop a dark-ground-positive sore like a chancre but at a different site from the original primary lesion. It becomes obvious in the clinic that these criteria are unsatisfactory too. The Sing Sing and other human experiments showed that the lesion of re-infection need not be dark-ground-positive nor quite "like a chancre". Ultimately, as Moore suggested, the differential diagnosis between relapse and re-infection must rest on clinical "hunches". In this context it is as well to remember that the more rigid the criteria for re-infection the less rigid are the criteria for relapse, which eventually is accepted as a self-evident truth. Self-evident truths seldom attract the attention of critical minds and I would suggest that failure to prove re-infection does not *ipso facto* prove relapse. The ultimate and so far unobtainable truth will depend on whether the spirochaetes responsible for a lesion have been derived from without or within, whether they are exogenous or endogenous.

My own clinical material was provided by the Seamen's Dispensary, Liverpool. Between January 1, 1931 and January 31, 1949, records were prepared for 11,911 male cases of syphilis, and a perusal of these showed 401 patients who presented two or more episodes of syphilis and whose second episodes (with one exception) showed as skin or mucous membrane lesions characteristic of early syphilis. 201 records were rejected for lack of real evidence that one episode really was syphilitic. This rejection invalidates any attempt at producing percentage figures, which in any case are not to my liking, for they teach but little. I attempted to analyse the remaining 200 case records of 189 patients, of whom 178 had two episodes (accounting for 178 cases) and eleven had

three episodes (accounting for 22 cases). No deliberate attempt was made to prove the efficacy of any one form of treatment but I was able to confirm the assertion of Ross (1945) that his particular treatment schedule, when assiduously undertaken, produced over 99 per cent. success in early syphilis. Rather was I more interested to learn when and in what circumstances second episodes occurred.

The series comprised 99 relapses, 45 re-infections, one superinfection, and 55 "indeterminates". For the latter, even a clinical hunch was not enough. I propose to refer to very few of the facts which emerged from the survey in order to reduce boredom to the minimum.

Of the 45 re-infections, 33 occurred in 1946, 1947, and 1948, following one year after the peak years for the incidence of syphilis, which were 1945, 1946, and 1947. One might be tempted to conclude that this incidence of re-infection was due to penicillin cutting short the development of immunity, but only thirteen of these 33 cases had had penicillin. Arsenic also cuts short the development of immunity. Although we had then no system of cross-reference for contacts and I was therefore unable to prove my point, my conviction was that "ping-pong" syphilis was the important factor at work. Schoch and Alexander (1943) drew attention to this. 24 re-infections were originally sero-positive primary cases, and ten were originally sero-negative primary cases, whereas the totals of first episodes were comparable (2,169 sero-negative, 2,690 sero-positive). Only three re-infections occurred in 1,180 originally secondary cases. Likewise, more relapses followed sero-positive than sero-negative primary cases. Stokes, Usilton, Cole, Moore, O'Leary, Wile, Parran, and McMullen (1934) drew attention to this phenomenon and suggested that the spirochaetes are better entrenched in these cases and that there is little immunity as yet. In sero-negative primary cases the spirochaetes are more easily eradicated by treatment. In secondary cases immunity is more advanced. I would agree with this if my own sero-positive primary re-infections had really been monorecidives, which I suppose they may well have been, but I am inclined to the view that, in sero-positive primary syphilis, before humoral anti-bodies play their part, the tissues have become more sensitive to spirochaetes than in sero-negative primary cases.

The majority of second episodes occurred in patients treated within the first year of infection (83 of 99 relapses, 43 of 45 re-infections). The majority of relapses (83) occurred within 2 years of the original infection. This is in accord with the findings of 93 per cent. by Stokes, Schoch, and Ireland (1931) and of 84 per cent. by Moore (1945). Re-infections, on

the other hand, occurred over a period extending from 1 month to 22 years, albeit 50 per cent. of them came within 3 years. These figures refer to all early cases, however originally treated, but it seems relevant for us as venereologists to note that all relapses following primary and secondary syphilis originally treated with penicillin alone occurred within 9 months of the start of treatment. This lends support to the growing tendency to discharge at least seronegative primary cases after one year's surveillance.

Whether a second episode following primary syphilis was a relapse or a re-infection, the average incubation period of the first episode was 3 weeks, the average duration of lesions before treatment began was  $2\frac{1}{2}$  weeks, and therefore the average duration of infection was  $5\frac{1}{2}$  weeks. It is therefore concluded that, if the degree of immunity as judged by the duration of infection falls short of that required to protect the skin, then the skin is as susceptible to exogenous as to endogenous spirochaetes, whether or not the patient has been cured. If uncured, the patient's own spirochaetes are ready to pounce. If cured or uncured, other people's spirochaetes are there to be risked.

#### Lesions encountered in Re-infection and Relapse

If the skin immunity in syphilis either fails to develop, as in a treated early primary case, or, having developed, falls sufficiently to permit a reaction to re-infection, then we should expect on re-infection to find a single lesion at the point of entry of the spirochaetes. When a similar lack of immunity occurs in an inadequately-treated person, we should expect the relapsing lesions to be multiple, because in these cases there has usually already been a dissemination of spirochaetes.

In re-infection we do in fact usually find a single primary lesion unless the case presents in the secondary stage, in which case we look for and expect to find that it has been heralded by a primary sore. In relapse we do usually find multiple lesions, either typical of early secondary syphilis and specified as macular, maculo-papular, papulo-nodular, and erythematofollicular rashes, and condylomata or mucous patches in the mouth or on the genitalia; or these relapsing lesions are of the late secondary variety such as annular, corymbous, rupial, pustular, framboesiform, or psoriasiform eruptions. If we give no more thought to the differential diagnosis than to a recognition of these facts, then we shall not go wrong very often.

There are many exceptions to these generalizations and confusion arises in the clinic,

- (a) When relapsing lesions are single, as typified by a re-induration of the original primary, *i.e.* the monorecive or chancre redux; by the non-ulcerating solitary papule; and, much later, by the pseudo-chancre redux which is gummatous.
- (b) When the lesions of re-infection are multiple, as with multiple primaries. This is uncommon.

In the differential diagnosis of re-infection versus relapse or even super-infection, each case has to be considered on its own merits and the final decision—if such there be—rests on one of Moore's "hunches". Time is too short to discuss all the possibilities and problems raised by all the different lesions found in second episodes. Perhaps for the clinician the subject is purely academic. A patient with a second episode needs treatment and his recent consort or consorts need to be examined and treated if necessary. If we could only prove a patient to have been cured of the first episode, then the second episode would be *ipso facto* a re-infection. But from our own point of view as physicians, we are intensely interested to know whether our routine treatment is adequate. To-day, few would dispute that, say, 3 weeks' non-stop penicillin cures early syphilis. Following such treatment, if we do come across second episodes, these are likely to present as single dark-ground-positive lesions and to be re-infections. But what of the monorecive?

It is understandable that a mono-recive occurring in a patient who has been treated for primary syphilis should itself be followed by secondary manifestations if allowed to proceed, for in this case the rest of the skin has not as yet reacted. Where a monorecive follows secondary syphilis, our understanding of the process becomes more cloudy. It is difficult to conceive the idea of immunity in an uncured patient, who has passed through the secondary stage, falling to such an extent that it permits a reactivation of spirochaetes at the site of the original primary sore, without, at the same time or earlier, permitting reactivation of spirochaetes elsewhere. The severity of the tissue reaction at the site of the primary sore has been greater than the reaction at the site of a secondary macule and we should expect immunity at the primary site to be greater rather than less than at the site of any one macule. By way of explanation it has been supposed that a few viable spirochaetes may at times become encased by fibrous tissue within the primary chancre. Subsequent trauma liberates these spirochaetes and a fresh reaction takes place. If such is the case then we must not only postulate but accept the fact that skin immunity to syphilis wanes. If it wanes at the site of the primary, then surely it must wane elsewhere.

We should not then be surprised to find a mono-recidive being followed by secondary lesions the result of a redissemination of spirochaetes, and indeed I have known this happen. Such a succession of events might be classed as a re-infection from within. In support of this theory I can recollect no case of a mono-recidive in which the records or my personal experience of the case showed there to have been complete clinical negativity, *i.e.* absence of induration, in the interval between the first and second episodes. This fact, no doubt, assisted in arriving at a diagnosis, but one may wonder whether many reported mono-recidives were not really re-infections. Absence of incontrovertible evidence in favour of re-infection will cause hesitancy in making a diagnosis. Peabody and Webster (1949) suggested that approximately 70 per cent. of recurrent attacks of syphilis are re-infections. This makes us raise our eyebrows, but we should not dismiss it as unwarranted. In my own series of 200 second episodes there were between 20 and 35 per cent. of re-infections, the higher figure being arrived at by adding half the indeterminate cases to the known re-infections. The concept of the monorecidive as a common clinical entity (13 per cent. of all relapses according to Stokes, Cole, and others (1931); 4 per cent. of my own relapse cases), is further diminished by the relative infrequency with which it follows an extragenital chancre. Stokes reported one on the finger 5 years after an original infection—this was followed by a sore throat—but I feel it could well have been a re-infection in one who practised a not uncommon method of sexual stimulation.

### Discussion

We have so far posed some problems and recalled the observed phenomena. Can we now attempt to account for them? Not, I think, without reference to tertiary syphilis. Nearly all attempts at an explanation of the refractoriness of the once-infected body to the subsequent inoculation of spirochaetes and of the differing degrees of reaction seen in the untreated patient, the chancre, the macule, and the gumma, have hitherto been based on the assumption that immunity to the spirochaete was an affair of the tissues. Allergy accounted for everything. Von Pirquet (1906) used the term "allergy" to denote an altered reactivity of the body in response to a foreign invasion. A diminished reactivity he called *hypoergie* and an increased reactivity *hyperergie*, terms already used by Neisser. For a clearer understanding of the allergic process in syphilis, we might with profit refer to the chancre, the mono-recidive, and the severe lesion of malignant syphilis as "syphilomata" or

"normo-syphilomata"; the macule and papule we might call "hypo-syphilomata", and the gumma a "hyper-syphiloma".

Thomas (1956), in an address entitled "The Challenge of Syphilis to Science", posed more problems than we can attempt to discuss here, and made reference to the possibility of a rhythmic alteration in tissue sensitivity but concluded that this was not all embracing. Nor was he satisfied that the TPI antibody could be invoked to account for protection, as was assumed after its discovery. We have already seen that a positive treponemal immobilization test may exist before the appearance of a second chancre. Despite this, it is my contention that either we are as yet insufficiently acquainted with the degree of TPI positivity or that the laboratory workers will discover more specific antibodies than are demonstrable by the TPI test.

Histologically, there is a basic similarity between the chancre, the macule or papule, and the gumma—the differences are of degree only. They are all examples not so much of what the spirochaete does to tissues but of what the tissues do about the spirochaete. Upon infection, there is no immediate inflammatory process as with virulent pyogenic organisms, and indeed throughout the natural history of the disease the patient and his spirochaetes appear to get on together. The patient suffers little or not at all from the mere presence of spirochaetes.

What the spirochaete does, as I see it, is to sensitize tissues and to provoke the formation of antibodies. It does the former at the site of inoculation during the incubation period, and elsewhere during the secondary incubation period. When duly sensitized, the tissues react, and the normal natural reaction is typified by the chancre and later by large condylomata. Having reacted, the tissues become insensitive and do not readily react again. "Chancre immunity" is an affair of the tissues and denotes tolerance of spirochaetes.

It used to be contended that this primary reaction conferred a degree of immunity on the rest of the body, so that the widespread dissemination of spirochaetes which had already occurred when the chancre erupts resulted only in minimal reactions *i.e.* the multiple small lesions of the secondary rash. How this immunity could be conferred by remote control, as it were, without postulating the presence of some humoral antibody circulating in the blood was left to our imagination. Eberson (1921) and Rich (1941), referring to the work of Turner (1939) and Turner, Fleming, and Brayton (1939), both claimed that such a humoral circulating antibody existed in syphilis but, as their work was not successfully repeated by others, it was ignored. In my



own pursuit of an explanation for the phenomena of syphilis, I came to the conclusion that Ebersson and Turner must be right, and in the process of saying so in 1949 in a lengthy unpublished paper of which this is a précis, Nelson and Mayer (1949) published the results of their experiments showing the existence of a treponemastatic or immobilizing antibody which is now demonstrated in the TPI test. Ebersson and Turner had demonstrated this antibody *in vivo*, Nelson and Mayer (1949) were the first to demonstrate it *in vitro*.

As the existence of this antibody is an accepted fact, there is little point in recalling all the arguments adduced against immunity in syphilis being an affair of the tissues only. But let one example suffice. The slow development of this antibody does not protect the patient from his secondary rash. The *T. pallida* landing in the skin sensitize the skin which then reacts, but each macule or papule does not develop to the proportions of a chancre. The immobilizing antibody arrives just in time and subsequently accounts for the disappearance of the rash. Had there been no humoral antibody, how could one explain the smallness of the papule by supposing it to be due to the reaction at the site of the chancre? It might be argued that fewer spirochaetes are responsible for a papule than are responsible for a chancre. If this is so, then the chancre has no right to be as large as it is. If there was no humoral antibody the lesions of secondary syphilis would each approximate to the chancre, and I believe this to be the case in malignant syphilis and, as just mentioned, in large condylomata.

### Conclusion

The paradox to which Neisser called attention is only an apparent one. Where immunity is non-existent or only slight then tissues are as responsive to exogenous as to endogenous spirochaetes. The infrequency of re-infection is to be accounted for by the small size of the inoculum of natural contagion and by its method of inoculation. I have long thought that the pseudo-chancre redux is, in some cases, the first lesion of re-infection in previously-sensitized and highly-sensitized tissue.

It is evident that spirochaetes sensitize tissue and that tissues—having reacted—become less sensitive. If the sensitizing process continues without a reaction, then the tissues become hypersensitive. Whether a reaction takes place or not would seem to depend on the degree of activity of spirochaetes which is controlled by the degree of humoral resistance. Non-sterilizing treatment interferes seriously with the development of humoral antibodies. I have seen a primary of the penis and a contiguous gumma of

the thigh in the same patient at the same time. He was a defaulter. Had he been adequately treated no lesion would have developed on the thigh. Had he received no treatment he would have developed a "kissing" chancre.

The various phases of syphilis may thus be accounted for by the fluctuating state of tissue sensitivity on the one hand and the fluctuating state of humoral antibody on the other. These processes would appear to be independent of each other, but are both dependent on the activity of spirochaetes. It is obvious that immunity to spirochaetes wanes with the passage of time. Tertiary lesions themselves stand witness to this fact. If tissues remain insensitive to spirochaetes, asymptomatic re-infection is a possibility not to be ignored and some cases of serological relapse might well be examples of this. I think, too, that we must accept spontaneous cure as a natural phenomenon, but if it is not, then latency for life surely is. And in this event we are driven to accept the notion propounded by others that some spirochaetes manage to get themselves sealed off. I doubt that they are in suspended animation. It would seem more probable that, though sealed off from the effects of antibody and may be of penicillin, they must multiply and a few escape from bondage. These in turn must succumb to antibody but not without first having "topped up", as it were, the formation of more antibody.

There must be infinite grades of tissue sensitivity, ranging from insensitivity through normal sensitivity and reverting to hypo-sensitivity or progressing to hyper-sensitivity. The state of the tissues determines the type of clinical reaction. The tissues will only react if spirochaetes are active. The activity of spirochaetes depends upon the degree of circulating humoral antibody. There must be infinite grades of humoral resistance. With no humoral resistance activity of spirochaetes is inevitable, with low humoral resistance activity is possible and probable, and with high humoral resistance activity is impossible or improbable. These assertions are illustrated in the accompanying Table (overleaf).

Whatever the degree of humoral antibody, if there is cellular insensitivity, no active lesions of the skin or mucous membranes will be seen. Whatever the state of cellular sensitivity, if there is high humoral resistance there will likewise be no active visible lesions. Outside the heavy lines of the diagram we are entirely dependent on the laboratory, inside the heavy lines we are permitted to use our clinical judgment coupled with the aid of a microscope and a battery of serological tests.

We have seen that spirochaetes sensitize tissues and provoke an antibody response. In a proportion

TABLE  
SUGGESTED RELATIONSHIP OF VARIOUS CLINICAL PHENOMENA OF SYPHILIS TO (a) THE STATE OF TISSUE SENSITIVITY AND  
(b) THE STATE OF CIRCULATING ANTIBODIES.  
see text for fuller explanation

Humoral Resistance	None	Low	High
Activity of <i>T. pallidum</i>	Inevitable	Possible and Probable	Impossible
Cellular Insensitivity	Incubation Asymptomatic infection Asymptomatic re-infection	Serological relapse Asymptomatic re-infection	Early latency Late latency Spontaneous cure
Cellular Sensitivity	Primary Syphilis Re-infection Large condylomata Malignant Syphilis Syphilitic pemphigus	Monorecivide Severe infectious relapse Re-infection	Late latency
	Secondary Syphilis Neo-natal rash		
Cellular Hyposensitivity	Re-infection with minimal sore	Solitary papule Mild infectious relapse	Early latency Late latency Spontaneous cure
Cellular Hypersensitivity	Pseudo-chancres redux (exogenous) Macerated foetus	Gumma Pseudo-chancres redux (endogenous)	Late latency

of cases they cause the exquisitely chronic fibrosis of late cardio-vascular syphilis and parenchymatous neurosyphilis, and produce that clinical museum piece, the syphilitic marasmic infant. I have excluded these from the discussion even though they denote the reaction of the body to spirochaetes. But they are the killers and would seem to be somewhat remote from the immunological processes.

When contemplating our syphilis patients we can say with D. H. Lawrence:

"You are all these, and on me lies the duty  
To see you all, sordid or radiant tissues."

### Summary

- (1) The problem posed by the relationship between the clinical phenomena and the immune processes in syphilis is set forth.
- (2) A summary is given of (a) historical observations with reference to conflicting concepts of the nature of immunity in syphilis, (b) animal experiments, (c) human experiments.
- (3) The problem of re-infection *versus* relapse as seen in the clinic is discussed, with particular reference to 200 second episodes seen at the Seamen's Dispensary, Liverpool.
- (4) The lesions of re-infection and relapse are discussed in greater detail.
- (5) An attempt is made to account for the various phenomena of syphilis by relating infinite grades of tissue sensitivity with infinite grades of circulating antibodies. It is suggested that

these are independent of each other although they both result from the activity of spirochaetes.

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## Phénomènes immunologiques de la syphilis

## RÉSUMÉ

- (1) On pose la question de la relation entre les aspects cliniques et immunologiques de la syphilis.
- (2) On passe en revue l'histoire des idées contradictoires d'immunité syphilitique, les expériences avec les animaux de laboratoire et ceux avec les sujets humains.
- (3) On discute le problème de ré-infection et de rechute, en ce qui concerne 200 malades qui se présentèrent une deuxième fois à la dispensaire des marins à Liverpool.
- (4) On décrit en détail les lésions typiques de ré-infection et de rechute.
- (5) On explique les symptômes divers de la syphilis par un comparaison des stades nombreux de la sensibilité tissulaire avec les anticorps infiniment divers du sang. Il se peut que ces deux facteurs sont complètement indépendants l'un de l'autre, même qu'ils se produisent tout deux de l'activité des spirochètes.

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